THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: WALLACH et al

Application No.: 08/485,129

Filed: June 7, 1995

For: ISOLATED DNA ENCODING TUMOR NECROSIS FACTOR ...

Art Unit: 1644

Examiner: R. Schwadron

Washington, D.C.

Atty.'s Docket: WALLACH=5B

Date: December 27, 1999

THE COMMISSIONER OF PATENTS AND TRADEMARKS

Washington, D.C. 20231

Sir:

Transmitted herewith is a [ ] Amendment [XX] BRIEF ON APPEAL with Appendix A; copy of Revised Interim Guidelines; and copy of front page and claims of USP 4,652,525 and 4,431,740 in the above-identified application.

[ ] Small entity status of this application under 37 CFR 1.9 and 1.27 has been established by a verified statement previously submitted.

[ ] A verified statement to establish small entity status under 37 CFR 1.9 and 1.27 is enclosed.

[ ] No additional fee is required.

The fee has been calculated as shown below:

	(Col. 1) CLAIMS REMAINING AFTER AMENDMENT		(Col. 2) HIGHEST NO. PREVIOUSLY PAID FOR	(Col. 3) PRESENT EXTRA	SMALL ENTITY RATE	SMALL ENTITY ADDITIONAL FEE	OR	OTHER THAN A SMALL ENTITY RATE	OTHER THAN A SMALL ENTITY ADDITIONAL FEE
TOTAL	*	MINUS	* *	=	x 9	$		x 18	$
INDEP.	*	MINUS	* * *	=	x 39	$		x 78	$
FIRST PRESENTATION OF MULTIPLE DEP. CLAIM					+130	$		+ 260	$
					TOTAL ADDITIONAL FEE	$	OR	TOTAL	

* If the entry in Col. 1 is less than the entry in Col. 2, write "0" in Col. 3.

** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 20, write "20" in this space.

*** If the "Highest Number Previously Paid For" IN THIS SPACE is less than 3, write "3" in this space.

The "Highest Number Previously Paid For" (total or independent) is the highest number found from the equivalent box in Col. 1 of a prior amendment of the number of claims originally filed.

[XX] Conditional Petition for Extension of Time

If any extension of time for a response is required applicant requests that this be considered a petition therefor.

[XX] It is hereby petitioned for an extension of time in accordance with 37 CFR 1.136(a). The appropriate fee required by 37 CFR 1.17 is calculated as shown below:

Small Entity Response Filed Within		Other Than Small Entity Response Filed Within	
[ ] First	- $ 55.00	[ ] First	- $ 110.00
[ ] Second	- $190.00	[XX] Second	- $ 380.00
[ ] Third	- $435.00	[ ] Third	- $ 870.00
[ ] Fourth	- $680.00	[ ] Fourth	- $1360.00
Month After Time Period Set		Month After Time Period Set	

[ ] Less fees ($_____) already paid for __ month(s) extension of time on _____.

[ ] Please charge my Deposit Account No. 02-4035 in the amount of $_____.

[XX] $300 Government fee for filing of appeal brief.

[XX] A check in the amount of $680.00 is attached (check no. 24432).

[XX] The Commissioner is hereby authorized and requested to charge any additional fees which may be required in connection with this application or credit any overpayment to Deposit Account No. 02-4035. This authorization and request is not limited to payment of all fees associated with this communication, including any Extension of Time fee, not covered by check or specific authorization, but is also intended to include all fees for the presentation of extra claims under 37 CFR Section 1.16 and all patent processing fees under 37 CFR Section 1.17 throughout the prosecution of the case. This blanket authorization does not include patent issue fees under 37 CFR Section 1.18.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

#27
AGJ
12/30/99

In re Application of:	Art Unit: 1644
WALLACH et al	Examiner: R. Schwadron
Appln. No.: 08/485,129	Washington, D.C.
Filed: June 7, 1995	December 27, 1999
For: ISOLATED DNA ENCODING TUMOR NECROSIS FACTOR BINDING PROTEIN II, AND VECTORS, HOSTS AND PROCESSES USING SUCH DNA	Atty.Docket: WALLACH=5B

BRIEF ON APPEAL

Honorable Commissioner of Patents and Trademarks
Washington, D.C. 20231

Sir:

Submitted herewith is applicant's Brief on Appeal in triplicate.

The present appeal is taken from the action of the examiner in finally rejecting claims 11-13, 35-38, 43, 44, 46-49 and 51. The full text of claims 11-13, 35-38, 43, 44, 46-49 and 51 under appeal appears in Appendix A attached hereto.

REAL PARTY IN INTEREST

The present application is owned by Yeda Research and Development Co. Ltd., which is the research and development arm of the Weizmann Institute of Science in Rehovot, Israel. The exclusive licensee of the present invention is Inter-Lab Limited, an Israeli company of Ness-Ziona, Israel. Inter-Lab Limited is a subsidiary of InterPharm Laboratories Limited, an Israeli company

of Ness-Ziona, Israel, which is a subsidiary of Ares Serono N.V., whose parent company, Ares Serono S.A., is a holding company under which there are many subsidiaries worldwide.

RELATED APPEALS AND INTERFERENCES

Appellant is aware of no other appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the present appeal.

STATUS OF CLAIMS

Claims 11-14, 35-39 and 43-51 presently appear in this case. Claims 11-13, 35-38, 43, 44, 46-49 and 51 are under final rejection. Claims 34 and 40-42 have been canceled. Claims 14, 39, 45 and 50 have been withdrawn from consideration, but it is understood that in the event that the claims on appeal are found allowable, these withdrawn claims will be treated as per MPEP §821.04.

STATUS OF AMENDMENTS

Subsequent to the final rejection of February 26, 1999, applicant filed an amendment on May 25, 1999, and a supplemental communication submitting three certified Israel priority documents on July 8, 1999. By Advisory Action of August 20, 1999, the examiner indicated that upon filing of an appeal, the proposed amendment would be entered. The examiner also entered and considered the supplemental communication and the Israeli priority documents.

SUMMARY OF THE INVENTION

The present invention is directed to isolated DNA molecules which encode Tumor Necrosis Factor (TNF) Binding Protein II (TBP-II). The protein encoded by the DNA of the present invention was initially isolated from human urine and was found to have the ability of selectively inhibiting the cytotoxic effect of TNF. Under certain conditions it can also act as a carrier for TNF and thus maintain its prolonged beneficial effects.

This naturally occurring protein TBP-II, which was isolated from the urine, was found to include the following partial amino acid sequence: Thr-Pro-Tyr-Ala-Pro-Glu-Pro-Gly-Ser-Thr in the portion of the protein sequenced by N-terminal sequence analysis.

The TBP-II encoded by the DNA of the present invention derived from human urine concentrate showed an apparent molecular weight of 30 kD in reducing SDS-PAGE analysis.

The DNA of the present invention may also encode active fractions of TBP-II provided the fraction has the ability to inhibit the cytotoxic effect of TNF.

The present claims are drawn to the isolated DNA molecules which encode the newly discovered TBP-II protein and active fragments thereof as well as replicable expression vehicles containing such DNA, host cells transformed with the replicable expression vehicle and processes for producing TBP-II by culturing such a transformant host cell.

One claim directed to the TBP-II protein was officially found to be allowable by the examiner in charge of the parent application. The claims drawn to the TBP-II protein in the parent application, 07/930,443, are now involved in an interference proceeding with the claims of U.S. patent 5,344,915.

THE PRIOR ART

The only prior art rejection in this case appearing in the final rejection of February 26, 1999, was withdrawn by the Advisory Action of August 20, 1999. Thus, there is no prior art which requires discussion in the present brief.

THE REJECTIONS

The rejection of claims 11-13 and 46-49 under 35 USC 112, first paragraph, as appearing in paragraph 17 of the final rejection was withdrawn in paragraph 2 of the Advisory Action of August 20, 1999. The rejection of claims 35, 43 and 44 under 35 USC 112, first paragraph, as appearing in paragraph 18 of the final rejection was withdrawn in paragraph 3 of the Advisory Action of August 20, 1999. The rejection of claims 11-13, 35-38, 43, 44 and 46-49 under 35 USC 102(e) as appearing in paragraph 21 of the final rejection was withdrawn in paragraph 5 of the Advisory Action of August 20, 1999. Thus, the only rejection remaining in this case for review in the present appeal is the rejection in paragraph 19 of the final rejection which was repeated in paragraph 4 of the Advisory Action of August 20, 1999.

The examiner's restatement of the rejection in this Advisory Action and his comments in response to applicants' arguments, which were not deemed persuasive, are as follows:

> Claims 11-13, 35-38, 43, 44, 46-49, 51 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons elaborated in the previous Office Action. Applicants arguments have been considered and deemed not persuasive.
>
> The specification does not provide adequate written description of the claimed invention. The legal standard for sufficiency of a patent's (or a specification's) written description is whether that description "reasonably conveys to the artisan that the inventor had possession at that time of the ... claimed subject matter", Vas-Cath, Inc. V. Mahurkar, 19 U.S.P.Q.2d 1111 (Fed. Cir. 1991). In the instant case, the specification does not convey to the artisan that the applicant had possession at the time of invention of the claimed DNAs and molecules containing said DNAs.
>
> The instant claims encompass an isolated DNA molecule or vectors or host cells which contain said DNA wherein said DNA encodes a protein consisting of naturally occurring TBP-II. There is no disclosure in the specification of an intact DNA sequence which encodes said molecule. There is no disclosure in the specification of any DNA sequence which encodes the claimed DNA. The claimed molecule recites physical features of a TBP-II protein and the amino acid sequences of a 10-13 amino acid sequence of the N terminal of a molecule that contains at least 250 amino acids. There is no disclosure in the specification of any DNA sequence which encodes the claimed molecule. In view of the aforementioned problems regarding description of the claimed

invention, the specification does not provide an adequate written description of the invention claimed herein. See The Regents of the University of California v. Eli Lilly and Company, 43 USPQ2d 1398,1404-7 (Fed. Cir. 1997). In University of California v. Eli Lilly and Co., 39 U.S.P.Q.2d 1225 (Fed. Cir. 1995) the inventors claimed a genus of DNA species encoding insulin in different vertebrates or mammals, but had only described a single species of cDNA which encoded rat insulin. The court held that only the nucleic acids species described in the specification (i.e. nucleic acids encoding rat insulin) met the description requirement and that the inventors were not entitled to a claim encompassing a genus of nucleic acids encoding insulin from other vertebrates, mammals or humans, id. at 1240. In the instant case, the specification has not provided even a single DNA sequence which encodes the claimed DNA. The Federal Circuit has held that if an inventor is "unable to envision the detailed constitution of a gene so as to distinguish it from other materials ... conception has not been achieved until reduction to practice has occurred", Amgen, Inc. v. Chugai Pharmaceutical Co, Ltd., 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991). Attention is also directed to the decision of The Regents of the University of California v. Eli Lilly and Company (CAFC, July 1997) wherein is stated: The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

Thus, as we have previously held, a cDNA is not defined or described by the mere name "cDNA," even if accompanied by the name of the protein that it encodes but requires a kind of specificity usually achieved by means of the recitation of the sequence of nucleotides that make up the cDNA. See Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606.

Regarding applicants comments in the instant amendment about the criterion C(2) from the interim written description guidelines, the following comments are made. The particular paragraph from C(2) which applicant quotes on page 14 of the instant amendment indicates that in order to meet the written description requirement the characteristics of the claimed invention need to be described "in such full, clear concise and exact terms that a skilled artisan would recognize applicant was in possession of the claimed invention". In the instant application, while applicant has disclosed information and methods to obtain the claimed nucleic acid sequence, applicant was clearly not in possession of the claimed invention at the time the instant application was filed. There is no disclosure in the specification of isolated nucleic acids encoding the molecule recited in the claims. Regarding the particular example from the interim written description guidelines which applicant quotes in page 15 of the instant amendment, said example differs from the instant application in that the example discloses a scenario wherein the applicant was in physical possession of the claimed molecule. In order to know that said molecule had the particular characteristics disclosed in said example, the molecule was isolated and demonstrated to have said characteristics. Therefore, applicant had physical possession of said molecule. It would be impossible to know the restriction and/or nuclease cleave sites without knowing the intact sequence of said nucleic acid or without having physically isolated the nucleic acid and empirically determined the information. In the case of the instant application, applicant has not demonstrated possession of the claimed

invention because while applicant has disclosed a method for isolating said molecule, the molecule was not isolated. Similarly, regarding the enzyme example listed in page 16 of the instant amendment, in order to determine the various physical properties recited in said claim, it was necessary to have already obtained and possessed said molecule. In the case of the instant application, applicant has not demonstrated possession of the claimed invention because while applicant has disclosed a method for isolating said molecule, the molecule was not isolated. Thus, the instant claims do not meet the criterion section C(2) from the interim written description guidelines. Regarding applicants theory that disclosure of a protein provides written description of the nucleic acid, there is no disclosure in the instant application of the amino acid sequence of TBP-II.

Regarding applicants comments in the instant amendment about University of California v. Eli Lilly, there is still no disclosure in the specification of any nucleic acid encoding the scope of the claimed invention (eg. a nucleic acid encoding TBP-II). There is also no disclosure in the specification of the amino acid sequence of intact TBP-II. While the specification discloses N-terminal amino acid sequence data indicating a possible partial amino acid sequence of 31 amino acids of TBP-II, said peptide contains at least 250 amino acids, wherein the identity of the vast majority of said amino acids has not been disclosed in the specification. In University of California v. Eli Lilly, the court held that only the nucleic acids species described in the specification (i.e. nucleic acids encoding rat insulin) met the description requirement and that the inventors were not entitled to a claim encompassing a genus of nucleic acids encoding insulin from other vertebrates, mammals or humans, Id. at 1240. In the instant case, the specification has not provided even a single DNA sequence which encodes the claimed DNA. The Federal Circuit has held that if an inventor is "unable to

envision the detailed constitution of a gene so as to distinguish it from other materials ... conception has not been achieved until reduction to practice has occurred", Amgen, Inc. v. Chugai Pharmaceutical Co, Ltd., 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991). Attention is also directed to the decision of The Regents of the University of California v. Eli Lilly and Company (CAFC, July 1997) wherein is stated: The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See In re Wilder, 736 F.2d 1516, 222 USPQ 369, 372-373 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, naming a type of material generally known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material.

Regarding applicants comments that TBP-II protein is disclosed in the specification and the intact amino acid sequence of TBP-II could be obtained using the methods disclosed in the specification, this is not the issue under consideration. The Federal Circuit has held that if an inventor is "unable to envision the detailed constitution of a gene so as to distinguish it from other materials ... conception has not been achieved until reduction to practice has occurred", Amgen, Inc. v. Chugai Pharmaceutical Co, Ltd., 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991). Clearly, in the instant application, the inventor is unable to envision the detailed constitution of a nucleic acid so as to distinguish it from other materials because the sequence of the claimed nucleic acid was not known to the inventors at the time of the filing date of the instant application. Regarding applicants comments about the TBP-II protein, none of the claims of the instant invention are drawn to TBP-II protein. The claims under consideration are drawn to nucleic acids. The possession of an isolated protein in itself

provides no written description of the identity of the nucleic acid encoding said protein in the absence of the complete amino acid sequence of said protein. Applicants response recites "Once the complete amino acid sequence is known, all contiguous DNA sequences which encode such a protein are known in view of the known rules of the genetic code.". However, the complete amino acid sequence of TBP-II is not disclosed in the instant application. The instant application merely recites methods that could be potentially used to elucidate the nature of said sequence. In the absence of the disclosure of the claimed nucleic acid in the specification or the complete amino acid sequence of TBP-II there is no written description of the scope of the claimed invention. Regarding applicants comments that University of California v. Eli Lilly only applies to "genes" per se, this not stated in University of California v. Eli Lilly. In fact, in University of California v. Eli Lilly the court clearly states that:

An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id. at 1170, 25 USPQ2d at 1606.

In the instant application, applicants has provided a plan and potential method for isolating the claimed nucleic acids, but have provided no written description of said nucleic acids.

ISSUE

The following issue is presented in this appeal:

Is there adequate written description for a claim covering all DNA sequences which encode a novel isolated protein defined by a partial amino acid sequence and other characterizing features?

GROUPING OF THE CLAIMS

All of the claims stand or fall together

ARGUMENT

The Patent Specification as Filed Describes the Claimed DNA in Sufficient Detail that One Skilled in the Art Can Reasonably Conclude that the Inventor Had Possession of the Claimed DNA

Applicant's position with respect to the written description rejection can be thumbnailed by the following syllogism.

1. The specification contains adequate written description for the TBP protein.

2. The complete amino acid sequence of a protein is an inherent property of an isolated protein. Therefore, even though the complete amino acid sequence was not explicitly disclosed, applicant was inherently in possession of the complete amino acid sequence.

3. Once one has demonstrated possession of the complete amino acid sequence, the genetic code automatically puts one in possession of all DNA sequences encoding that amino acid sequence. QED.

As to the first paragraph of the above syllogism, it is not believed that the examiner disputes the fact that there is written description for the TBP protein in the application as originally filed. It should be noted that during the prosecution of this case the examiner has not refuted this particular part of the syllogism. The examiner states at the beginning of the first full paragraph on page 4 of the Advisory Action of August 20, 1999:

> Regarding applicant's comments that TBP-II protein is disclosed in the specification and the intact amino acid sequence of TBP-II could be obtained using the method disclosed in the specification, this is not the issue under consideration.

The first paragraph of the syllogism is consistent with the Revised Interim Guidelines.[1] Section II.3.A.(1)(a)-(c) of these Guidelines states that, for original claims, for each claim drawn to a single species, one must first determine whether the application describes an actual reduction to practice of the claimed invention or if there is evidence of a completed invention by reduction to drawings. Section (c) goes on to state:

> If the application does not describe an actual reduction to practice or reduction to drawings, determine whether the invention has been set forth in terms of distinguishing identifying characteristics as evidenced by

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[1] Throughout this brief, "Revised Interim Guidelines" will refer to the "Revised Interim Guidelines for Examination of Patent Applications under the 35 U.S.C. §112, §1 'Written Description' Requirement", published in the Federal Register on December 21, 1999, at 64(244) 71427-71440. A copy of the Revised Interim Guidelines is attached hereto as Appendix B for the convenience of the Board.

> other descriptions of the invention that are sufficiently detailed to show that applicant was in possession of the claimed invention.

Here, with respect to the protein, there was an actual reduction to practice as the protein was actually isolated. Furthermore, the protein was described by a partial amino acid sequence and sufficient other distinguishing identifying characteristics that are sufficiently detailed to show that applicant was in possession of the claimed invention. The fact that the protein was adequately described to comply with the written description requirement is evidenced by the fact that at least one protein claim was allowed during the prosecution of the parent application 07/930,443, which is now involved in an interference proceeding with the claims of U.S. patent 5,344,915.

With respect to the second paragraph of the above syllogism, reference is made to Ex parte Yamaguchi, 6 USPQ2d 1805, 1807 (BdPatApp&Int 1987), where it states:

> Moreover, it is well settled that from a standpoint of patent law, a compound and all of its properties are inseparable. They are one and the same. *In re Papesch* 50, CCPA 1084, 315 F2d 381, 137 USPQ 43 (1963). In our view, the X-ray diffraction spectrum, like the graphic formulae, the chemical nomenclature, etc., is merely a symbol by which the compounds can be identified, classified and compared.

The same is true for the amino acid sequence of a protein.

See also Ex parte Marsili, 214 USPQ 904 (PTOBdApp 1979) which held that a change in the structural formula of a chemical compound that was adequately described in terms of its characteristics in the original specification did not violate the

description requirement. It is also noted that in the Board decision of Ex parte Deuel, 27 USPQ2d 1360, 1363 (BdPatApp&Int 1993), the Board noted the examiner's position that the amino acid sequence is an inherent characteristic of the protein.

In this case, in light of the partial amino acid sequence of the protein and the other characterizing features disclosed, as well as the method for obtaining the protein, one of ordinary skill in the art could obtain the entire amino acid sequence of the protein without undue experimentation.

As to the third paragraph of the syllogism, it is clear that the present DNA claims generically encompass all DNA sequences encoding naturally occurring human TBP-II. As the genetic code provides a direct relationship of amino acid sequences and associated nucleic acid codons, it is a scientific fact that given the complete amino acid sequence of a protein, coupled with knowledge of the genetic code, one is in possession of the genus of all of the DNA sequences which will encode that complete amino acid sequence. In re Deuel, 34 USPQ2d 1210, 1216 (Fed. Cir. 1995), noted that, with the aid of a computer, a person of ordinary skill in the art may even be able to identify all members of the claimed genus. Thus, if one is in possession of the complete amino acid sequence encoded by a claimed DNA sequence, then one is necessarily in possession of the entire claimed DNA genus.

As stated in the Revised Interim Guidelines in the second paragraph of Section I:

> To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient

> detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention.

Similarly, the last paragraph of Section I reads:

> The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed.

Thus, it is possession of the claimed invention which is important. The above syllogism establishes that applicant was in possession of the genus of DNA sequences that encode the single species of naturally occurring human TBP-II. As applicant was in possession of the invention as now claimed, the fundamental factual inquiry necessary to satisfy the written description requirement must be answered in the affirmative.

There is nothing in the case law cited by the examiner which precludes an applicant from claiming the genus of DNA which encodes an adequately disclosed protein. Admittedly, if the present claims were directed to the human cDNA encoding TBP-II, the case law would require a 35 USC 112, first paragraph, written description rejection because it would have been impossible for applicant to envision that single specific sequence which is the cDNA. Thus, even though there is written description in the present specification for the genus of all DNA sequences which encode a given amino acid sequence, there is admittedly no written description for the specific species of the cDNA, and indeed the specific species of the cDNA is not being specifically claimed in the present application. In the case relied upon by the examiner, discussed in detail hereinbelow, the claims being reviewed for

compliance with the written description requirement were directed to the cDNA and not to broad DNA claims covering any DNA sequence which encodes the novel protein. Indeed, in the case cited by the examiner, the protein was not novel and therefore a generic DNA claim, such as is presently claimed, would have been obvious.

More specifically, the examiner relies mainly on University of California v. Eli Lilly and Co., 43 USPQ2d 1398 (Fed. Cir. 1997). While that case relates to the infringement of two patents, i.e., patents 4,652,525 and 4,431,740 owned by the Regents of the University of California (UC), validity issues relating to the written description requirement of the first paragraph of 35 USC 112 were raised only with respect to the '525 patent. Copies of the front page and claims of these two patents are attached hereto as Appendices C and D. It can be seen that, in the '525 patent, all of the claims are directed to insulin-encoding cDNA, or the reverse transcript of mRNA which encodes insulin, which is synonymous with cDNA. Note that the Federal Circuit in the Lilly case at page 1405 characterizes claims 1 and 2 of the '525 patent as being claims "which *generically* recite cDNA encoding vertebrate insulin, and claim 4, which is directed *generically* to cDNA encoding mammalian insulin" [emphasis original] and that dependent claims 6 and 7 "similarly recite cDNA encoding vertebrate insulin." As to claim 5, the court stated, at pages 1404-1405:

> Claim 5 is directed to a recombinant prokaryotic microorganism modified so that it contains "a nucleotide sequence having the structure of the reverse transcript of an mRNA of a [human], which mRNA encodes insulin.

Thus, the definition of the claimed microorganism is one that requires human insulin-encoding cDNA. The validity of claim 3 was not before the court. Thus, it is very clear that all of the claims being construed for compliance with the written description requirement were claims directed to cDNA, i.e., the naturally occurring sequence which is only one of the myriad of possible sequences which encode human insulin due to the degeneracy of the genetic code. Therefore, the holdings in the Lilly case which require that the sequence of the cDNA be known before that cDNA can be in the possession of the inventors so as to satisfy the written description requirement, are all related to the specific situation before the court in which all that is being claimed is cDNAs, either a cDNA of a single species or a genus of cDNAs of a plurality of animal species.

In the Advisory Action of August 20, 1999, in response to applicant's previous arguments that the Lilly case applied only to cDNAs *per se*, the examiner refers to page 1404 of Lilly where it states:

> An adequate written description of a DNA, such as the cDNA of the recombinant plasmids and microorganisms of the '525 patent, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention.

However, when the DNA claim is written broadly so as to include all DNA which encodes a particular amino acid sequence, the description of the amino acid sequence or sufficient characterizing information to establish that applicant was in

possession of a novel protein, is sufficient to satisfy the requirement for a precise definition. Indeed, the examiner himself states at page 6 of the Advisory Action:

> In the absence of the disclosure of the claimed nucleic acid in the specification, or the complete amino acid sequence of TBP-II there is no written description of the scope of the claimed invention. [Emphasis added]

Thus, the examiner appears to admit that if applicant were in possession of the complete amino acid sequence of TBP-II, then applicant would automatically be in possession of the claimed nucleic acid sequence which anyone of ordinary skill in the art could write as a formula once the complete amino acid sequence is known. Indeed, reference is made to claim 5 of the '740 patent involved in the Lilly case in which such a DNA sequence broad enough to encompass all DNAs which encode human proinsulin is set forth. Such a formula can readily be prepared for any given amino acid sequence without any knowledge of the naturally occurring cDNA.

Reference is also made to footnote 13 of the Revised Interim Guidelines which explicitly states:

> [a] genetic code table would correlate a known amino acid sequence with a genus of coding nucleic acids ... .

Here, applicant readily admits that the specification does not contain a complete amino acid sequence of TBP-II. However, it does disclose a partial amino acid sequence and sufficient other characterizing features to establish that applicant was in possession of the protein. Indeed, applicant had isolated the protein. The written description requirement was

satisfied for the protein as is evidenced by the allowability of at least one protein claim in the parent application. As the complete amino acid sequence of a protein is an inherent property of an adequately described protein which is in possession of the applicant and a genetic code table can correlate any amino acid sequence with a genus of coding nucleic acids, it must necessarily follow that adequate written description of a protein is inherently an adequate written description of a broad DNA claim which encompasses all nucleotide sequences which encode that protein.

There is nothing in the Revised Interim Guidelines which mandates a rejection of the present claims under the written description requirement. Indeed, in the response to comment 6 at page 71429 of the Federal Register notice, the material accompanying these Guidelines makes clear that the Revised Interim Guidelines do not impose a *per se* requirement for reduction to practice in any technology to satisfy the written description requirement. The discussion goes on to state:

> However, the Federal Circuit has recognized that in some instances an inventor may only be able to establish a conception (and therefore possession) by pointing to a reduction to practice through a successful experiment. ... In such instances, the alleged conception fails not merely because the field is unpredictable or because of the general uncertainty surrounding experimental sciences, but because the conception is incomplete due to factual uncertainty that undermines the specificity of the inventor's idea of the invention.

Here, while applicant may not have reduced to practice a specific DNA, applicant has reduced to practice the protein. Applicant has possession of the protein and has provided adequate written description of the protein. The complete amino acid sequence of the protein is an inherent property of the protein. Because the formula of all DNA which encompass that amino acid sequence is dictated by the genetic code, i.e., is a fixed formula, the DNA sequence is as much an inherent property of the adequately described protein which has been reduced to practice as is the complete amino acid sequence thereof. Therefore, there is no actual uncertainty that undermines the specificity of the inventor's idea of the invention, such as would require an actual reduction to practice of a DNA before an applicant can be in possession thereof.

The statement in Section II.A.3 at the right column of page 71435 of the Federal Register notice is also applicable where it states:

> An applicant may also show that an invention is complete by disclosure of sufficiently detailed relevant identifying characteristics which provide evidence that applicant was in possession of the claimed invention, *i.e.*, complete or partial structure, other physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics.

Such sufficiently detailed relevant identifying characteristics have been provided in the present specification for the protein. As the complete amino acid sequence of the protein is an inherent characteristic of the protein and as the formula for DNA which

encodes the complete amino acid sequence is a fixed formula determined by the genetic code, such DNA formula is also an inherent characteristic of the adequately described protein.

Furthermore, the claims effectively include a partial nucleic acid sequence. All of the present claims recite at least 10 amino acid residues of the protein encoded by the DNA. Thus, at least 30 nucleotides of the DNA are disclosed. Regardless of the fact that the DNA molecule of the present invention is much longer than 30 nucleotides, this is an important unique bit of characterizing information. This piece of nucleotide structure, in conjunction with the characterizing information that the DNA encodes a protein having the ability to inhibit the cytotoxic effects of TNF, provides sufficient relevant identifying characteristics to comply with the criteria of the above-quoted portion of the Revised Interim Guidelines.

The same paragraph of the Revised Interim Guidelines goes on to state:

> If a skilled artisan would have understood the inventor to be in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate description requirement is met.

This sentence further supports the conclusion reached by the syllogism set forth hereinabove. Accordingly, for the reasons discussed in detail hereinabove, possession of a novel protein and a written description thereof sufficient to comply with the written description requirement of the first paragraph of 35 USC 112 inherently places one in possession of the formula of all DNA

which encodes that protein. As the complete amino acid sequence of that protein is an inherent property of the protein and the generic DNA sequence which encodes that amino acid sequence is directly correlatable therewith by means of a genetic code table, a holding that the present claims comply with the written description requirement would be fully consistent with the newly issued Revised Interim Guidelines. Reversal of the examiner and withdrawal of this rejection are therefore respectfully urged.

CONCLUSION

The claims as submitted are believed to truly set forth the inventive concept of the present invention and to fully comply with the written description requirement of the first paragraph of 35 USC 112. Accordingly, reversal of the examiner and allowance of claims 11-13, 35-38, 43, 44, 46-49 and 51 are earnestly solicited.

Respectfully submitted,

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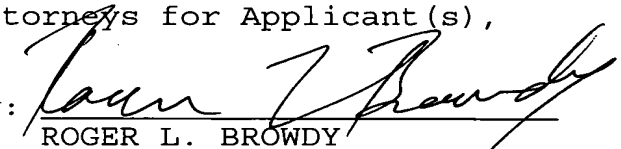
Attorneys for Applicant(s),

By: 

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APPENDIX A

11. An isolated DNA molecule comprising a contiguous nucleotide sequence coding for a protein consisting of naturally occurring human Tumor Necrosis Factor (TNF) Binding Protein II, herein designated TBP-II, said TBP-II including the amino acid sequence: Thr-Pro-Tyr-Ala-Pro-Glu-Pro-Gly-Ser-Thr in the portion of the protein sequenced by N-terminal sequence analysis, said protein having the ability to inhibit the cytotoxic effect of TNF, wherein said naturally occurring TBP-II protein is the same as that protein having the ability to inhibit the cytotoxic effect of TNF which, after being purified by subjecting a crude protein recovered from a dialyzed concentrate of human urine to affinity chromatography on a column of immobilized TNF, elutes from a reversed-phase high pressure liquid chromatography column as a single peak in a fraction corresponding to about 31% acetonitrile and shows a molecular weight of about 30 kDa when measured by SDS-PAGE under reducing conditions.

12. A replicable expression vehicle comprising the DNA molecule of claim 11 and capable, in a transformant host cell, of expressing said protein.

13. A host cell selected from the group consisting of a prokaryotic and a eukaryotic cell transformed with the replicable expression vehicle of claim 12.

35. An isolated DNA molecule in accordance with claim 51, comprising

(1) the nucleotide sequence coding for a naturally occurring human Tumor Necrosis Factor (TNF) binding protein (TBP-II) having the following characteristics:

i. includes the amino acid sequence Thr-Pro-Tyr-Ala-Pro-Glu-Pro-Gly- Ser-Thr in the portion of the protein sequenced by N-terminal sequence analysis; and

ii. the ability to inhibit the cytotoxic effect of TNF-α on murine A9 cells, or

(2) a contiguous nucleotide sequence coding for a fragment of said TBP-II which has the ability to inhibit the cytotoxic effect of TNF-α on murine A9 cells.

36. An isolated DNA molecule comprising

(1) the nucleotide sequence coding for a naturally occurring human Tumor Necrosis Factor (TNF) binding protein (TBP-II) having the following characteristics:

i. includes the amino acid sequence Thr-Pro-Tyr-Ala-Pro-Glu-Pro-Gly- Ser-Thr in the portion of the protein sequenced by N-terminal sequence analysis; and

ii. the ability to inhibit the cytotoxic effect of TNF-α on murine A9 cells; and

iii. a molecular weight of about 30kd in reducing SDS-PAGE analysis, or

(2) a contiguous nucleotide sequence coding for a fragment of said TBP-II which has the ability to inhibit the cytotoxic effect of TNF-α on murine A9 cells.

37. A replicable expression vehicle comprising the DNA molecule of claim 51 and capable, in a transformant host cell, of expressing said protein.

38. A host cell selected from the group consisting of a prokaryotic and a eukaryotic cell transformed with the replicable expression vehicle of claim 37.

43. A replicable expression vehicle comprising the DNA molecule of claim 35 and capable, in a transformant host cell, of expressing said protein.

44. A host cell selected from the group consisting of a prokaryotic and a eukaryotic cell transformed with the replicable expression vehicle of claim 43.

46. An isolated DNA molecule comprising (1) a contiguous nucleotide sequence coding for a protein consisting of naturally occurring human Tumor Necrosis Factor (TNF) Binding Protein II, herein designated TBP-II, said TBP-II including the amino acid sequence: Thr-Pro-Tyr-Ala-Pro-Glu-Pro-Gly-Ser-Thr in

the portion of the protein sequenced by N-terminal sequence analysis, said protein having the ability to inhibit the cytotoxic effect of TNF, wherein said naturally occurring TBP-II protein is the same as that protein having the ability to inhibit the cytotoxic effect of TNF which, after being purified by subjecting a crude protein recovered from a dialyzed concentrate of human urine to affinity chromatography on a column of immobilized TNF, elutes from a reversed-phase high pressure liquid chromatography column as a single peak in a fraction corresponding to about 31% acetonitrile and shows a molecular weight of about 30 kDa when measured by SDS-PAGE under reducing conditions, or (2) a contiguous nucleotide sequence coding for a fragment of said TBP-II which has the ability to inhibit the cytotoxic effect of TNF.

47. An isolated DNA molecule in accordance with claim 51, wherein said nucleotide sequence is the sequence of (2).

48. A replicable expression vehicle comprising the DNA molecule of claim 47 and capable, in a transformant host cell, of expressing said protein.

49. A host cell selected from the group consisting of a prokaryotic and a eukaryotic cell transformed with the replicable expression vehicle of claim 48.

51. An isolated DNA molecule comprising

(1) a contiguous nucleotide sequence coding for a naturally occurring human Tumor Necrosis Factor (TNF) binding protein (TBP-II) having the following characteristics:

(a) includes the amino acid sequence Thr-Pro-Tyr-Ala-Pro-Glu-Pro-Gly-Ser-Thr in the portion of the protein sequenced by N-terminal sequence analysis; and

(b) has the ability to inhibit the cytotoxic effect of TNF; or

(2) a contiguous nucleotide sequence coding for a fragment of said TBP-II which has the ability to inhibit the cytotoxic effect of TNF.

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